

Controlled Release Pharmaceutical Compositions With Improved Bioavailability**Field of invention**

The present invention relates to controlled release oral pharmaceutical compositions
5 with improved bioavailability having at least one active pharmaceutical ingredient of low
bioavailability. In particular, the present invention relates to a controlled release
pharmaceutical composition where its bioavailability is improved by solubilizing the active
ingredient using a solubilizer and incorporating it in a gastro-retentive system.

10 Background of the Invention

Certain pharmaceutical active agents are not easily absorbed from the
gastrointestinal tract or do not dissolve readily in the medium of gastrointestinal tract. For
such pharmaceuticals, bioavailability is usually low and unfortunately creates a need for
frequent dosing of a large amount of the pharmaceutical in order to provide and maintain
15 therapeutic levels. The need for frequent dosing presents patient compliance problems and
the need for large amount of active ingredient may result in increased toxicity.

For pharmaceuticals whose bioavailability is limited by solubility or dissolution rate
various attempts have been made in the prior art to improve solubility or dissolution rate. In
US Patent No. 4,973,469 ('469 patent) a process of preparing a controlled release
20 formulation by preparing an adsorbate of drug and inactive substance on to copovidone
(copolymer of N-vinyl-2-pyrrolidone and vinyl acetate) is described. According to the '469
patent, a water-insoluble inactive substance serves to impede the rate of dissolution whereas
a water-soluble substance would result in leaching of drug adsorbed on the crosslinked
polymer. The '469 patent however, does not disclose any method or composition to increase
25 the solubility of the drug which is very important for increasing bioavailability of poorly
soluble drugs.

In US Patent No. 6,699,503 ('503 patent) a hydrogel type sustained release
preparation is disclosed comprising at least one drug, an additive which insures penetration
of water into the core of the preparation and a hydrogel forming polymer. Due to the
30 presence of a hygroscopic agent that pulls water into the preparation a gel is formed and the
release of the drug is apparently enhanced. Unfortunately, the pulling of water into the
system using hygroscopic agent does not necessarily ensure increase in dissolution rate or
release of poorly soluble drug.

In US Patent No. 5,945,125 ('125 patent), a controlled release tablet formulation containing a pharmaceutical agent and a water-swellable polymer is disclosed such that a zero order release rate is achieved. While this disclosure aims to achieve a zero order controlled release formulation, it does not attempt to increase bioavailability of the active
5 agent.

All the above prior approaches are primarily aimed at process for enhancing or retarding the release of an active pharmaceutical ingredient or a process of achieving a specific dissolution profile. Unfortunately, mere increases in dissolution rate may not ensure improved bioavailability as solubility of the drug is not altered. These prior
10 approaches do not result in the reduction in dose of a drug and associated benefits such as reduction in side effects, patient compliance etc.

In US Patent No. 5,736,161 ('161 patent) methods and composition are disclosed for improving the oral absorption of drug by means of encapsulation in millispheres of gellable hydrocollids covered with positively charged polysaccharide. Unfortunately, the
15 processes involved in the preparation of millispheres and encapsulation of drugs therein are tedious, expensive and difficult to produce on a commercial scale.

In WO03000294 a pharmaceutical composition with a solid dispersion of a low solubility drug and a matrix forming agent combined with a polymer is disclosed. A major portion of the drug is in the amorphous form. The composition apparently provides
20 improved solubility, bioavailability and stability of the active ingredient. Also a method of achieving controlled release of the active in amorphous form is described. The WO03000294 disclosure is not suitable for drugs having a narrow window of absorption as only part of the drug will be released near the absorption window and remaining drug would be lost unabsorbed.

25 In US Patent No. 6,107,276 ('276 patent) pharmaceutical compositions of slightly soluble drugs are described. The composition includes a surface active agent and an oil in which the drug is dispersed which is adsorbed on to crospovidone (crosslinked polyvinyl pyrrolidone). This apparently results in improved dissolution and consequently improved bioavailability. The formulation may also be adopted for controlled release of the
30 solubilized active. However, this approach is not suitable for drugs which are only absorbed in the upper segments of gastrointestinal tract.

As seen from the prior approaches, though various methods such as complexation, change in crystalline form of drug or preparation of micro-emulsion etc are made to

increase the solubility of the low solubility drug. Unfortunately, many of these processes encounter difficulties during commercial scale manufacture. Some of these concepts have been utilized further to formulate controlled release oral dosage forms. A controlled release of a solubilized drug will only result in substantial improvement of bioavailability for drugs 5 that are absorbed throughout the gastrointestinal tract. These prior approaches have proven not to be useful for drugs having a narrow window of absorption in the gastrointestinal tract, which demands the release of solubilized drug at or near the site of absorption in order to achieve improved bioavailability.

US Patent No. 5,780,057 ('507 patent) describes a pharmaceutical dosage form for 10 oral administration comprising of 2 or 3 layer tablets where at least one layer can rapidly swell by contact with biological and/ or aqueous fluids, said swelling resulting in a considerable increase in the tablet volume resulting in gastric retention. The '507 patent discloses a dosage form allowing a slow release of the active ingredient to the stomach and/or the first tract of the intestines. This multilayered system is useful only for 15 pharmaceutical active ingredients having high aqueous solubility. For pharmaceuticals having low solubility, release from such a system would be prolonged to an extent that a sizeable amount of drug would remain unreleased.

US Patent No. 6,340,475 ('475 patent), describes a water soluble drug formulated as 20 unit dosage form by incorporating it into polymeric matrices comprised of hydrophilic polymer that swell upon imbibing water, to a size that is large enough to promote retention of the dosage form in the stomach during the fed mode. While it is helpful that the delivery system be adapted to remain in the stomach for a prolonged period, it is important that the system deliver active agent in a controlled manner. Unfortunately, these systems would not be suitable for low solubility pharmaceuticals as the release of these would be dramatically 25 retarded from such systems.

US Patent No. 6,120,803 describes compositions where the dosage form of the active agent is a polymer matrix that swells upon contact with fluid of stomach. A portion of the polymer matrix is surrounded by a band of insoluble material that prevents the concerned portion of polymer matrix from swelling and provides a segment of the dosage 30 form that is of sufficient rigidity to withstand the environment of the stomach and delay expulsion of the dosage form from the stomach until substantially all of the active agent has been dispersed. This disclosure describes a special kind of gastroretentive system with a

polymer band of insoluble material. Application of such a band on the tablets needs special equipment and is difficult to produce on a commercial scale.

US Patent No. 6,022,562 discloses microcapsules for oral administration of medicinal and nutritional active principles which are smaller than 1000 µm and which are 5 claimed to remain in the small intestine for a longer time (at least 5 hrs) allowing for the release and absorption of the active principles. Although these microcapsules are claimed to remain in the intestine for long duration, they would be emptied rather rapidly from stomach and upper gastrointestinal tract, the main site of drug absorption..

It is thus evident that many prior attempts have been made to formulate gastro-retentive compositions utilizing various techniques like increasing the size of the tablets 10 after ingestion, or inclusion of a non-swellable band, or a bio-adhesive composition, or preparation of microspheres. In these systems the active agent is released by diffusion or a combination of diffusion and erosion. The majority of the prior approaches are with water-soluble active agents where due to high solubility, the drug is released by diffusion over a 15 desired length of time.

It is a significant challenge to develop a gastroretentive system for poorly soluble drugs where release of drug through diffusion is restricted by solubility of the drug. Poor solubility may result in prolongation of release beyond the retention time and loss of unabsorbed drug. Some of the prior approaches describe eroding matrices, however, it 20 would be still difficult to achieve a balance between the desired release of the drug through erosion and gastroretention as they are mutually antagonistic.

It has been surprisingly found that when a solubilized drug is incorporated in gastroretentive system the desired delicate balance of release and retention could be achieved. The present invention describes the compositions of sparingly soluble drugs 25 having improved instantaneous solubility. These solubilized drugs when formulated in a controlled release swelling matrix, achieve more than 80% drug release in 12 hrs in dissolution studies; this was not possible to attain when such drugs were available in either only solubilized compositions or only controlled release compositions as such. Increase in solubility and release of drug near absorption site ensures better absorption of the drug 30 resulting in increased bioavailability. Increased bioavailability coupled with extended released would mean reduction in dose, dosage frequency, improved patient compliance and more importantly enhanced therapeutic benefits.

Summary of the Invention

In accordance with the present invention, controlled release of the drug with improved bioavailability, reduction in dose, reduction in dosage frequency, reduction in undesirable side effects and improved patient compliance are achieved by combining 5 solubilization of low solubility drugs with gastro-retention.

Thus according to an aspect of the present invention there is provided a controlled release oral pharmaceutical composition comprised of a therapeutically effective amount of one or more pharmacologically active agent having low bioavailability; one or more solubilizers; one or more biocompatible swelling agents; and a swelling enhancer wherein 10 the swelling agent, in combination with swelling enhancer, swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide retention of the dosage form in the stomach of a patient, and gradually erode within the gastrointestinal tract over a prolonged time period.

An object of the present invention is to provide controlled release pharmaceutical 15 compositions for oral administration having at least one active pharmaceutical ingredient of low bioavailability due to low aqueous solubility and/or limited absorption in the gastrointestinal tract wherein its instantaneous solubility is increased prior to controlling its release.

Another object of the present invention is to solubilize low solubility drugs and 20 further utilize the solubilized drugs to formulate controlled release compositions to effectively increase their bioavailability.

Yet another object of the present invention is to provide a simple and cost effective controlled release pharmaceutical composition, for improved bioavailability which would be simple and cost efficient to manufacture on a commercial scale.

A further object of the present invention is to provide gastroretentive compositions 25 that are retained in the stomach for a longer period of time thereby increasing the bioavailability of drugs with limited absorption.

Another object of the present invention is to provide a controlled release pharmaceutical composition that has reduced level of dose frequency and therefore 30 improved patient compliance.

Yet a further object of the present invention is to combine increased solubilization of drug with greater gastro-retention achieving controlled release of a low solubility drug,

improved bioavailability, reduction in dose level, reduction in dosage frequency, reduction in undesirable side effects and improved patient compliance.

Another object of the invention is to provide a multi-layered tablet having either an instant release layer and a gastroretentive sustained release layer, or one or more 5 gastroretentive sustained release layers.

Yet further object of the present invention is to provide a gastro-retentive composition which has increased solubility and the release of drug near absorption site to ensure better absorption of the drug resulting in increased bioavailability which coupled with extended release would result in the reduction in dose, dosage frequency, improved 10 patient compliance and more importantly enhanced therapeutic benefits.

According to another aspect of the present invention there is provided a gastro retentive oral pharmaceutical dosage form in the form of an expanding multilayered system comprising an instant release layer having one or more active ingredients in a solubilized form and at least one additional layer having one or more active ingredients for controlled 15 drug delivery, one or more solubilizers, one or more biocompatible swelling agents and a swelling enhancer.

According to another aspect of the present invention there is provided a gastro retentive oral pharmaceutical dosage form in the form of an expanding multilayered system comprising two or more sustained release layers having one or more active ingredients in a 20 solubilized form in each layer. Each of the sustained release layers contains one or more active ingredients for controlled drug delivery, one or more solubilizers, one or more biocompatible swelling agents and a swelling enhancer.

Another object of the present invention is to provide a gastro-retentive composition with a solubilizer and a swelling enhancer, in the form of an expanding multilayered system 25 for oral administration. The composition is adapted to deliver an active agent from a first layer immediately upon reaching the gastrointestinal tract and deliver same or different agent from a second layer, in a controlled manner over a specific time period, the second layer is also adapted to provide expanding dosage form, thereby effectively retaining the dosage form in the stomach.

Brief Description of the Drawings

The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative embodiments, taken in conjunction with the accompanying drawings in which:

5 FIG. 1 is a graphic depiction of an in vitro dissolution study of acyclovir solubilized using various solubilizers;

FIG. 2 is a graphic depiction of In vitro dissolution of Acyclovir tablets; and

FIG. 3 graphically shows that incorporation of a solubilizer increases dissolution rate of the acyclovir, which results in an increase in bioavailability.

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Detailed Description of Invention

The present invention comprises the preparation and use of a solubilized low solubility drug in a sustained release, gastro-retentive system wherein the maximum amount of drug will be available for absorption by virtue of its solubilized property and continuous release through the gastro-retentive system.

15 The invention is particularly useful for drugs having a narrow therapeutic window of absorption wherein gastro-retention employed according to the invention allows a continuous trickling of solubilized drug thereby maximizing bioavailability of the drug. Accordingly the present invention provides for two components for formulating the controlled release composition:

20 *Solubilization of the drug:* - The low solubility drugs are solubilized using surface active agents like hydrophilic surfactants, lipophilic surfactants or mixtures thereof.

25 *Gastro-retention of the drug:-* The solubilized drug is then incorporated in a gastro-retentive matrix system, which remains in the stomach by virtue of its size after swelling and allows a slow and continuous release of the solubilized drug which helps in increasing the extent of drug absorption and improving bioavailability.

SOLUBILIZATION OF THE DRUG:

According to this invention, the increase in instantaneous solubility of the drug is achieved by using one or more suitable solubilizers. The low solubility drug and one or more solubilizers may be employed in different ratios. The selection of ratio depends upon the properties of the active ingredient, the desired improvement in its solubility and the type of solubilizers employed. It is contemplated within the scope of the invention that the ratio of drug: solubilizers can range from about 20 :1 to about 1:20. The preferred ratio of drug:

solubilizers ranges from about 10 :1 to about 1 :10. The most preferred ratio being about 5:1 to about 1:5. A combination of solubilizers may also be included wherein the total amount of solubilizer employed is maintained in the above-mentioned ratios.

Different non-limiting processes may be employed to prepare a solid solution of the drug and solubilizer or to form a physical mixture so as to increase the solubility of the active ingredient. It is contemplated within the scope of the invention that the processes may include solubilization using melt granulation or solvent treatment method. In case of melt granulation, the solubilizer is melted and the drug is added and mixed with the molten mass effectively, allowed to solidify and the granules are separated from each other. In another illustrative embodiment of this system the drug is granulated using molten solubilizer. In some cases drug and solubilizer both may be melted together and cooled to room temperature.

In using a solvent treatment method, either the solubilizers or the drug, or both are dissolved in a solvent and the solvent is then evaporated. The resultant mass is a blend of drug and solubilizer, such that the solubility of the drug is increased. Solvent employed in this system may be aqueous or non-aqueous depending on the solubility of the drug and solubilizer.

It is contemplated within the scope of the invention that a combination of hot melt process and solvent treatment method can be employed. In this case the drug may be initially granulated with one or more molten solubilizer which can be further treated with a same /different solubilizer in a solvent or visa versa.

It is also contemplated within the scope of the invention that any process known in the art suitable for solubilization of drugs may be employed for the purpose of this invention.

Melt granulation and intimate physical mixture are the most preferred methods for solubilization of the drug, according to this invention. The increase in solubility can be determined by studying the actual solubility studies of the drug in presence of solubilizer or it can also be determined by carrying out dissolution studies in an appropriate dissolution medium. The dissolution method is preferred as it allows for calculation of the rate of dissolution by determining the amount of drug dissolved at different time intervals

GASTRO-RETENTION OF DRUG:

According to the invention an additional component of the inventive system comprises increased gastro-retention. A number of gastro-retentive sustained release systems are reported in the literature. The following three major approaches describe 5 gastroretentive controlled release devices that may be employed according to the invention:

Floating or buoyant system: These systems have low density enabling them to float on gastric contents after their administration until the system either disintegrates, or the device absorbs fluid to the point where its density increases to an extent that it loses buoyancy and can then pass more easily from the stomach;

10 **Bioadhesive system:-** This system is designed to imbibe fluid following their administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucous/ mucus layer; and

15 **Swelling and expanding system:** - These systems are designed to be sufficiently small on administration allowing for easy ingestion, but after ingestion rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has occurred.

20 Floating or buoyant systems require special techniques to decrease density of the dosage form or contain certain gas generating agent. These systems therefore are larger in size and do not allow use of high dosages of drugs. It is difficult to achieve bioadhesion in the gastric mucosa due to the large amount of fluid present in the stomach and also the gastric motility through the housekeeper wave that causes dislodgement of the dosage form. In one illustrative embodiment according to the invention a swelling and expanding system is employed. It is contemplated within the scope of the invention that other approaches for 25 gastro-retention, namely floating and bioadhesive system or the like may be used.

25 In a first illustrative embodiment, a controlled release, gastro-retentive swelling system incorporating solubilized drug is contemplated. The controlled release gastro-retentive swelling system according to the invention employs a combination of polymers, which swell voluminously in the presence of gastric contents to increase the dosage form size such that it precludes its passage through the pylorus.

30 According to the invention it has been surprisingly found that addition of swelling enhancers to the gastro-retentive swelling system reduces the swelling time considerably which can further aid in improving bio-availability of drugs with narrow therapeutic absorption window.

The dosage form of the present invention is a solid dosage form, preferably a tablet, which may vary in shape including but not limited to oval, triangle, almond, peanut, parallelogram, pentagonal. It is contemplated within the scope of the invention that the dosage form can be encapsulated.

5 Tablets in accordance with the invention may be manufactured using conventional techniques of common tableting methods known in the art such as direct compression, wet granulation, dry granulation and extrusion/ melt granulation.

10 The dosage form according to the invention may include excipients conventionally known in art such as filler, binders and lubricants. Fillers such as lactose monohydrate, microcrystalline cellulose, dicalcium phosphate or the like may be used. Binders like polyvinyl pyrrolidone (PVP), copovidone or the like may be used. Lubricants such as Aerosil-200, magnesium stearate and hydrogenated vegetable oils and triglycerides of stearic acid, palmitic acid or the like may be utilized.

15 In one illustrative embodiment according to the invention, the dosage form may be optionally coated. Surface coatings may be employed for aesthetic purposes or for dimensionally stabilizing the compressed dosage form. The surface coating may be any conventional coating which is suitable for enteral use. The coating may be carried out using any conventional technique employing conventional ingredients. A surface coating can for example be obtained using a quick-dissolving film using conventional polymers such as 20 hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, polyvinyl alcohol poly methacrylates or the like.

25 In a further illustrative embodiment a solid pharmaceutical composition in the form of an expanding multilayer system for oral administration is adapted to deliver an active pharmaceutical agent from a first layer immediately upon reaching the gastrointestinal tract, and to deliver a further pharmaceutical agent which may be same or different from a second layer, in a controlled manner over a specific time period. The second layer is also adapted to provide expanding nature for the dosage system, thereby making the dosage system have greater retention in the stomach.

30 In this further illustrative embodiment a solid pharmaceutical composition for oral administration contains two or more layers comprising of an instant release (IR) layer comprising an active ingredient, filler such as lactose, microcrystalline cellulose and disintegrant such as croscarmellose sodium, a lubricant such as magnesium stearate, and

optionally other excipients and other active ingredients. The pharmaceutical active agent in this instant release layer may be present in a solubilized form.

The pharmaceutical composition according to this illustrative embodiment further contains at least one second layer, which is referred to as a controlled release layer (CRL) 5 that includes one or more pharmaceutical active agent for controlled drug delivery, one or more solubilizers, one or more biocompatible swelling agent and a swelling enhancer. The swelling agent, in combination with swelling enhancer, swells in presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide retention of the dosage form in the stomach of a patient, and gradually erode within the 10 gastrointestinal tract over a prolonged time period.

The disintegrating agent present in the first layer (IR) can be selected from a group including but not limited to the following: starch, sodium starch glycolate, pregelatinised starch, crosslinked poly vinyl pyrrolidone, cross linked carboxy methyl cellulose, ion exchange resin, the most preferred being sodium starch glycolate. Sodium starch glycolate 15 is present in an amount ranging from about 0.25% to about 10%, more preferably about 0.5 to about 5.0% and most preferably about 1% by weight based on the total weight of the composition.

Each of these layers may contain an active pharmaceutical ingredient, with the ratio 20 of the active ingredient in the first layer (IR) to the active ingredient in the second layer (CRL) being in the range of from about 10:90 to about 90:10 by weight. It is contemplated within the scope of the invention that these layers may contain the same or different active pharmaceutical ingredients such that one of the active ingredient is in the form of instant release dosage form whereas the other may be in the controlled release form.

In a further illustrative embodiment a solid pharmaceutical composition in the form 25 of an expanding multilayer system for oral administration is adapted to deliver at least two active agents present in different layers in a controlled manner over a specific time period.

The dosage form having either a single layer or multi-layer composition will after 30 ingestion gradually swell upon contact with gastric fluid. The time taken for swelling may vary from about 15 min to about 4 hours preferably within about 15 min to about 3 hours and most preferably within about 15 min to about 2 hours. The shorter axis of the dosage form has to expand to a length of more than about 0.8 cm and preferably more than about 1.0 cm.

Pharmacologically active agent:

The pharmacologically active agents according to the invention are those having low bioavailability. It is contemplated within the scope of the invention, however, that any pharmaceutical active ingredient may be used. The low bioavailability can be because of 5 low solubility and/or limited oral absorption or a narrow therapeutic absorption window. The active agents may be selected, but not limited to, one of the following therapeutic classes of active substances that includes: antiulcer, antidiabetic, anticoagulant, antithrombic, hypolipaemic, antiarrhythmic, vasodilatory, antianginal, antihypertensive, and 10 vasoprotective agents, fertility enhancers, labour inducers and inhibitors, and contraceptive, antibiotic, antifungal, antiviral, anticancer, anti-inflammatory, analgesic, antiepileptic, antiparkinsonian, neuroleptic, hypnotic, anxiolytic, psychostimulatory, antimigraine, antidepressant, antitussive, antihistamine and antiallergic agents.

The active pharmaceutical agents may be selected, but not limited to, pentoxyfylline, prazosin, acyclovir, levodopa, nifedipine, diltiazem, naproxen, flurbiprofen, ketoprofen, 15 fenoprofen, fentiazac, oestradiol valerate, metoprolol, sulpiride, captopril, cimetidine, zidovudine, nicardipine, terfenadine, salbutamol, carbamazepine, ranitidine, enalapril, simvastatin, fluoxetine, famotidine, ganciclovir, famiciclovir, valaciclovir ciprofloxacin pentazocine, omeprazole, saquinavir, ritonavir, nelfinavir, thiamphenicol, clarithromycin, azithromycin, ceftazidime, cyclosporine, digoxin, paclitaxel, iron salts, eprosartan, losartan 20 potassium, valsartan, candesartan, topiramate, ketoconazole and mixtures thereof.

Solubilizer:

In accordance with features of the present invention, the solubilizer acts to increase the instantaneous solubility of the pharmaceutically active agent. The solubilizer may be selected from hydrophilic surfactants or lipophilic surfactants or mixtures thereof. The 25 surfactants may be anionic, nonionic, cationic, and zwitterionic surfactants.

The hydrophilic non-ionic surfactants may be selected from the group comprised of, but not limited to: polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils preferably glycerol, ethylene 30 glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide, d- α -tocopheryl polyethylene glycol 1000 succinate.

The ionic surfactants may be selected from the group comprised of, but not limited to: alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids,

oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

The lipophilic surfactants may be selected from the group comprised of, but not limited to: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; PEG sorbitan fatty acid esters, PEG glycerol fatty acid esters, polyglycerized fatty acid, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters; and mixtures thereof.

Preferably the solubilizer may be selected from PEG-20-glyceryl stearate (Capmul® by Abitec), PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), PEG 6 corn oil (Labrafil® by Gattefosse), lauryl macrogol – 32 glyceride (Gelucire 44/14® by Gattefosse) stearoyl macrogol glyceride (Gelucire 50/13® by Gattefosse), polyglyceryl – 10 mono dioleate (Caprol ® PEG 860 by Abitec), propylene glycol oleate (Lutrol ® by BASF), Propylene glycol dioctanoate (Captex® by Abitec) Propylene glycol caprylate/caprate (Labrafac® by Gattefosse), Glyceryl monooleate (Peceol® by Gattefosse), Glycerol monolinoleate (Maisine ® by Gattefosse), Glycerol monostearate (Capmul® by Abitec), PEG- 20 sorbitan monolaurate (Tween 20® by ICI), PEG – 4 lauryl ether (Brij 30® by ICI), Sucrose distearate (Sucroester 7® by Gattefosse), Sucrose monopalmitate (Sucroester 15® by Gattefosse), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series BASF), polyethylene glycol 660 hydroxystearate, (Solutol® by BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, Dioctyl sulphosuccinate, L- hydroxypropyl cellulose, hydroxylethylcellulose, hydroxy propylcellulose, Propylene glycol alginate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, betains , polyethylene glycol

(Carbowax® by DOW), d- α -tocopheryl polyethylene glycol 1000 succinate. (Vitamin E TPGS® by Eastman) and mixtures thereof.

A more preferred solubilizer may be selected from PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), lauryl macrogol – 32 glyceride (Gelucire 44/14® by 5 Gattefosse) stearoyl macrogol glyceride (Gelucire 50/13® by Gattefosse), PEG- 20 sorbitan monolaurate (Tween 20® by ICI), PEG – 4 lauryl ether (Brij 30® by ICI), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, polyethylene glycol (Carbowax® by DOW) and mixtures thereof.

10 **Biocompatible swelling agent:**

The swelling agent used in the present invention includes one or more swellable biocompatible hydrophilic polymers. Preferably, the polymers are employed in the dry state or in a form that has substantial capacity for water uptake.

Water-soluble polymers used as swelling agents that are useful in preparation of the 15 said composition of this invention are polymers that are nontoxic and swell in a dimensionally unrestricted manner upon imbibition of gastric fluid. Examples of polymers which can be used include but are not limited to: polyalkylene oxides; cellulosic polymers; acrylic acid and methacrylic acid polymers, and esters thereof, maleic anhydride polymers; polymaleic acid; poly(acrylamides); poly(olefinic alcohol)s; poly(N-vinyl lactams); polyols; 20 polyoxyethylated saccharides; polyoxazolines; polyvinylamines; polyvinylacetates; polyimines; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; zein; shellac-based polymers; polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid, 25 maltodextrin, pre-gelatinized starch and polyvinyl alcohol, copolymers and mixtures thereof.

One or more hydrophilic polymers are preferably selected from the group consisting 30 of polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid, maltodextrin, pre-gelatinized starch, polyvinyl alcohol and mixtures thereof.

One or more hydrophilic polymers are more preferably a polyalkylene oxide selected from the group consisting of poly(ethylene oxide), poly(ethylene oxide-co-propylene oxide), and mixtures thereof.

One or more hydrophilic polymers are most preferably poly(ethylene oxide). At 5 least one of the biocompatible hydrophilic polymer has an average molecular weight in the range of about 5,000 to about 20,000,000.

The weight percent of the hydrophilic polymer in the dosage form is about 5 to about 90 weight percent, preferably about 10 to about 70 weight percent, and most preferably about 15 to about 50 weight percent.

10 **Swelling enhancers:**

15 Swelling enhancers are members of a special category of excipients that swell rapidly to a large extent resulting in a dramatic increase in the size of the tablet. At lower concentrations, these excipients are used as superdisintegrants; however at concentration above 5 % w/w these agents function as swelling enhancers and help increase the size of the dosage form.

According to the invention swelling enhancers include but are not limited to: low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal magnesium-aluminum silicate, corn starch granules, rice starch granules, potato starch granules, pregelatinised starch and sodium carboxymethyl starch.

20 According to the invention the swelling enhancer is preferably cross-linked polyvinyl pyrrolidone. The content of the swelling enhancer is about 5 to about 90 weight percent preferably about 10 to about 70 weight percent, most preferably about 15 to about 25 50 weight percent.

The composition according to the invention may make use of a single polymer alone or a combination of polymers with or without a swelling enhancer as required. When a combination of polymers and a swelling enhancer is employed for gastro-retention, the swelling enhancer allows a rapid and dramatic increase in the size of the tablets.

30 The swelling enhancer cannot maintain the integrity of the dosage form and avoid its disintegration and polymers may not show the rapid increase in size desired for gastro-retention by themselves alone due to their slow rate of swelling. Therefore, a synergistic combination may preferably be employed which allows rapid swelling by virtue of the

presence of swelling enhancer and maintenance of integrity by polymeric network formed by swelling of the polymer(s).

Thus the invention describes a unique combination of technologies wherein a solubilized drug is incorporated into a swelling matrix of polymer(s) and swelling enhancer 5 to achieve gastro-retention. Controlled release is thus achieved by; integrity of the matrix and the need for the gastric fluid to diffuse into the matrix or is achieved by controlled rate of erosion of the matrix, and the need for the matrix to erode in order to release much of the drug or a combination of the two.

The gastro-retentive controlled release compositions according to the invention 10 includes a solubilized drug that finds utility when administered to patients in the fed or the fasting mode. The fed mode is preferred since the narrowing of the pyloric opening that occurs in the fed mode serves as a further means of promoting gastric retention by retaining a broader range of size of the dosage form. Following oral administration to a patient, the dosage form is retained in the upper gastrointestinal tract for a time period of about 30 min 15 to about 12 hours or about 1 hour to about 9 hours or most preferably about 1 hour to about 6 hours.

While the present invention has been described in terms of its specific illustrative 20 embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to non-limiting exemplary illustrations

Example 1:

Swelling studies:

In this example various polymer placebo tablets were prepared at a polymer concentration 25 of 20% w/w and the rate of swelling was determined in 0.1N HCl

Table 1

Swelling of various polymer tablets

Sr. No	Polymers	Swelling in 50 ml 0.1 N HCl				
		15 min	1 Hrs	2 Hrs	3 Hrs	4 hrs
1.	Xanthan Gum	18.8x 8 mm	20x10mm	21x11mm	21x12mm	21x12mm
2.	Polyethylene oxide	18.8x 8 mm	20x10mm	21x11 mm	21x12mm	21x12 mm

	(Sentry Polyox WSR 1105)			with slight erosion	with slight erosion	with erosion
3.	Polyethylene oxide (Sentry Polyox WSR 60K)	18.8x 8 mm	20x10mm	21x12 mm	21x13 mm	21x13 mm
4.	Polyethylene oxide (Sentry Polyox WSR 301)	18.8x 8 mm	20x10mm	21x12 mm	21x12 mm	21x13 mm
5.	Hydroxypropyl methylcellulose (Methocel K100)	18.8x 8 mm	19x9 mm	20x10 mm	21x11 mm	22x12 mm
6.	Hydroxypropyl methylcellulose (Methocel K100 M)	18.8x 8 mm	19x9 mm	20x10 mm	21x11 mm	22x12 mm
7.	Hydroxypropyl methylcellulose (Methocel K4M)	18.8x 8 mm	19x10 mm	20x10 mm	21x11 mm	22x12 mm

The study showed that among various polymers polyoxyethylenes exhibited a maximum rate of swelling. Although, these polymers alone can be used for gastro-retentive drug delivery systems, there is a need to further increase the rate of swelling.

5 **Example 2:**

Swelling studies of tablets containing Swelling Enhancers

In this example swelling enhancers, namely crospovidone, crosscarmellose sodium, sodium starch glycolate and starch 1500, were incorporated into a placebo tablet at a concentration

of about 10% w/w. However these agents resulted in too rapid and voluminous swelling of the dosage forms leading to their disintegration.

Example 3:

5 ***Swelling studies of tablets containing combination of polymers and swelling enhancers***

A combination of swelling enhancer and a matrix forming polymer were incorporated in a placebo tablet. Table 2 shows the rates of swelling for these dosage forms.

Table: 2

Swelling data of tablets containing combination of polymers and swelling enhancers

Sr. No.	Polymer / swelling enhancer	15 min	60 min	120 min
1	Polyethylene oxide (Sentry Polyox WSR 60K) / Crospovidone (1:1.5)	18.8x 8 mm	22 x12 mm with erosion	22 x13 mm with erosion
2	Polyethylene oxide (Sentry Polyox WSR 60K) /Crospovidone (1:1)	18.8x 8 mm	22 x13 mm with slight erosion	22 x13 mm with slight erosion
3	Polyethylene oxide (Sentry Polyox WSR 60K) / Crospovidone (1.5:1)	18.8x 8 mm	22 x13 mm with slight erosion	22 x13 mm with slight erosion
4	Hydroxypropyl methylcellulose (Methocel K100M)/	18.8x 8 mm	20 x 10 mm	21 x 11 mm

	Crospovidone (1.5 :1)			
5	Hydroxypropyl methylcellulose (Methocel K4M) / Crospovidone (1.5 :1)	18.8x 8 mm	20 x 11 mm	22 x 11 mm

Example 3 shows that the combination of a swelling enhancer and polymer results in dosage form with a faster rate of swelling, as desired for gastro-retention.

Example 4:

5 ***Solubilization of drug using various solubilizing agents:***

A solubilizing agent was melted in a container and a drug was added and mixed intimately and cooled to room temperature. The mass was sifted through an appropriate sieve to get a uniform blend. A blend of the drug was prepared using polyethylene glycol 6000, Lutrol F127 and Gelucire (50/13). Solid dispersion of the drug with various solubilizing agents 10 like polyethylene glycol 6000, Lutrol F127 and Gelucire 50/13 were studied for their solubility in 900 ml distilled water.

Acyclovir in a ratio of (1:1 and 1:5) with polyethylene glycol 6000 showed a two-fold increase in solubility, acyclovir in ratio of (1:0.5 to 1:1) with Gelucire 50/13 showed a 5 fold increase in instantaneous solubility against acyclovir as such. Also with Lutrol in ratio 15 (1:0.5 to 1:2) a three-fold increase in instantaneous solubility was observed. These samples were taken for dissolution study and the result obtained are provided in Table 3 hereunder and graphically depicted in Figure-I:

Table 3:

In vitro dissolution study of acyclovir solubilized using various solubilizers

Time in min	Acyclovir as is (% drug dissolved)	Acyclovir :PEG (% drug dissolved)	Acyclovir : Lutrol (% drug dissolved)	Acyclovir : Gelucire %dissolved
0	0	0	0	0
5	16.03	55.38	74.34	97.25
10	19.58	64.79	83.16	100.96

15	24.09	71.46	85.77	
20	29.34	77.85	88.49	
30	33.89	81.32	94.57	
45	47.11	84.30	97.22	
60	53.78	85.64	99.06	
90	68.87	87.45	98.86	
120	75.40	92.67	99.13	

As would be evident from the above data, we may conclude that use of solubilizing agents increases the instantaneous solubility of the low-solubility drugs like Acyclovir.

5 Example 5:

Gastroretentive tablets of Acyclovir

The solubilized drug was further used for formulating controlled release tablets. Based on the solubility data it was decided to use the combination of Acyclovir : Gelucire 50 /13 for the preparation of the tablets.

10 Table 4:

Composition of acyclovir tablets with and without solubiliser

Ingredients	A (Mg/tablet)	B (Mg/tablet)
Acyclovir	250.00	250.00
Stearoyl macrogol glyceride (Gelucire 50/13®)	50.00	-
Polyethylene oxide (Sentry Polyox WSR 60K)	300.00	300.00
Crospovidone	350.00	350.00
Polyvinyl pyrrolidone K30 (PVP)	50.00	50.00

K30)		
Magnesium stearate	10.00	10.00

Gelucire was melted and acyclovir was granulated with molten gelucire. These granules of acyclovir were further granulated with polymers using PVP K30. Granules were dried and lubricated and further compressed into tablets using a compression machine. In case of 5 formulation B drug was mixed with polymers and granulated and similar procedure was further followed.

Dissolution condition:

Dissolution medium : 0.1N HCl
 10 Volume of the dissolution medium : 900 ml
 Temperature : 37°C

The results obtained are represented hereunder in Table V and graphically depicted in Figure-II:

15 **Table 5:**

In vitro dissolution of Acyclovir tablets

Time intervals (hr)	Tablet with solubilized drug	Tablet with unsolubilized drug
0	0.00	0.00
2	20.89	30.95
4	36.90	43.57
8	66.73	63.39
10	84.59	69.72
12	97.04	75.81
14	-	78.04

Example 6***In vivo study***

5 In vivo study was carried out to determine the relative bioavailability of Acyclovir from the test formulation of Example 5 (Acyclovir 250 mg tablets) in comparison to the reference formulation Zovirax® (Acyclovir 200 mg tablets). The study was open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, and comparative oral bioavailability study in healthy, adult, male human subjects (n=4) under non-fasting conditions. The blood levels were monitored over 24 hours time period.

Table 6**10 *In vivo data***

No.	Formulation	AUC _{0→∞} (ng.h/mL)
1	Reference	2624.96
2	Test product	5920.23

The data indicate that there is significant increase in the bioavailability of the formulation of the present invention compared to the reference product.

Example 7:**15 Azithromycin formulation*****Table 7******Composition of Azithromycin tablets***

Ingredients	Mg/tablet
Azithromycin	250.00
Polyoxyethylene polypropylene block copolymer (Lutrol F68)	125.00
Hydroxy propyl methylcellulose (Methocel K100M)	80.00
Hydroxyethyl cellulose (Natrosol HF)	80.00
Sodium starch glycolate (Primojel)	200.00

Microcrystalline cellulose (Avicel PH102)	250.00
Polyvinyl pyrrolidone K30 (PVP K30)	50.00
Magnesium stearate	10.00

Lutrol was melted and azithromycin was added to the molten Lutrol forming a dispersion. The dispersion was mixed and cooled while mixing to achieve a homogenous mass. Granules of azithromycin were further granulated with polymers using PVP K30.
 5 Granules were dried and lubricated and further compressed into tablets using a compression machine.

Example 8

Simvastatin formulation

10 *Table 8*

Composition of Simvastatin tablets

Ingredients	Mg/tablet
Simvastatin	80.00
Polyethylene glycol 6000 (Carbowax 6000)	160.00
Sodium carboxymethyl cellulose (Cekol 30000)	150.00
L-Hydroxy propyl cellulose (L-HPC)	130.00
Dicalcium phosphate	200.00
Lactose	250.00
Polyvinyl pyrrolidone	50.00
Magnesium stearate	10.00

Polyethylene glycol was melted and simvastatin was added to the molten Polyethylene glycol forming a dispersion. The dispersion was mixed and cooled while mixing to achieve a homogenous mass. Granules of drug were further granulated with
 15

polymers using PVP K30. Granules were dried and lubricated and further compressed into tablets using a compression machine.

Example 9

5 Carbamazepine formulation

Table 9

Composition of Carbamazepine tablets

Ingredients	Mg/tablet
Carbamazepine	200.00
Sodium lauryl sulphate	50.00
PEG 40 hydrogenated castor oil (Cremophor RH40)	50.00
Hydroxy propyl methylcellulose (Methocel K100M)	90.00
Sodium carboxymethyl cellulose (Cekol 30,000)	45.00
Alginic acid	135.00
Silicified microcrystalline cellulose (Prosolve 90)	400.00
Polyvinyl pyrrolidone K30 (PVP K30)	50.00
Magnesium stearate	10.00

10 Cremophor RH 40 was melted and sodium lauryl sulphate was dispersed in it and carbamazepine was added forming a dispersion. The dispersion was mixed and cooled while mixing to achieve a homogenous mass. Granules of drug were further granulated

with polymers using PVP K30. Granules were dried and lubricated and further compressed into tablets using a compression machine.

Example 10: Bilayered tablets of Acyclovir with and without solubilizer

5

Acyclovir SR component

Table 10: Composition of Acyclovir tablet sustained release layer

Ingredients	Mg/tablet	
	A	B
Acyclovir	200.00	200.00
Stearoyl macrogol glyceride (Gelucire 50/13®)	40.00	
Polyethylene oxide (Sentry Polyox WSR 60K)	240.00	240.00
Crospovidone	280.00	280.00
Polyvinyl pyrrolidone 30 K	50.00	50.00
Dextrates Dihydrate	220.00	220.00
Magnesium Stearate	10.00	10.00

Acyclovir IR component

10 ***Table 11:Composition of Acyclovir tablet immediate release layer***

Ingredients	Mg/tablet
Acyclovir	50.00
Microcrystalline cellulose (Avicel PH101)	52.50

Polyvinyl pyrrolidone 30 K	2.00
Sodium Starch Glycol ate (Primojel)	5.00
Magnesium Stearate	0.5

Preparation of sustained release granules (Formulation A):

Acyclovir was mixed with molten Gelucire50/13. This mixture was then blended with Polyethylene oxide WSR60K, Crospovidone, Dextrose Dihydrate. This blend was further granulated with Polyvinyl pyrrolidone 30K. The granules were dried and lubricated with Magnesium Stearate.

Preparation of sustained release granules (Formulation B):

Acyclovir was blended with Polyethylene oxide WSR60K, Crospovidone, Dextrose Dihydrate. This blend was further granulated with Polyvinyl pyrrolidone 30K. The granules are dried and lubricated with Magnesium Stearate.

Preparation of immediate release granules:

The IR component was prepared by granulating the drug along with microcrystalline cellulose using polyvinyl pyrrolidone-30K and lubricating with Sodium Starch Glycolate and Magnesium Stearate.

The SR component of formulation A and B and IR component were compressed together to form a double layer tablet. It is evident from Figure 3 that incorporation of a solubilizer increases dissolution rate of the acyclovir, which results in an increase in bioavailability.

It will be understood that various modifications may be made to the embodiments and examples disclosed herein. Therefore, the above description and examples should not be construed as limiting, but merely as exemplification of the various embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.